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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/501,787	02/11/2000	Laurent Coen	03495.0187	4369

22852 7590 01/12/2006

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EXAMINER	
BRANNOCK, MICHAEL T	
ART UNIT	**PAPER NUMBER**
1649	

DATE MAILED: 01/12/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/501,787	COEN ET AL.	
	Examiner	Art Unit	
	Michael Brannock	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 November 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5 and 8-37* is/are pending in the application.

4a) Of the above claim(s) *12-30 and 32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,8-11, 31, 33-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 May 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 12-30, 32, withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim, as set forth previously. Further, claims 1-5 and 8-11 are being examined only to the extent that the claims read on the in vivo delivery of a composition comprising fragment C of tetanus toxin plus at least 11 amino acids of fragment B. Further, claims 8-11, 31, 33-37 are being examined to the extent that they read on SMN protein, as set forth previously.

Maintained Rejections

Claims 1-5, 8, 11, 31, 34, 36 and 37 stand rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No: 5780024 in view of Halpern et al., Infection and Immunity, 58(4)1004-1009, April 1990, as set forth previously and reiterated below.

U.S. Patent No: 5780024 discloses an in vivo method for delivery (e.g. intramuscular, see col 4) of a composition (SOD:Tet451), comprising a the tetanus toxin C fragment recombinantly fused to a second protein (e.g. SOD-1, see the Abstract), wherein said second protein is fused downstream to the tetanus toxin C fragment (see col 6) and wherein the fusion protein is capable of in vivo retrograde axonal transport and transynaptic transport in to the CNS (e.g. from systemic administration to the brain stem, see col 1). Further, U.S. Patent No: 5780024 disclosed that the method can be used in the treatment of neurodegenerative diseases of the CNS (see col 1 for example).

U.S. Patent No: 5780024 discloses that the tetanus toxin C fragment used in the method of delivery can include additional amino acids, see col 6, as a matter of routine optimization of operating perimeters; yet U.S. Patent No: 5780024 does not disclose, specifically, that the C-fragment should contain at least 11 amino acids of the B-fragment nor that the there should be exactly 11 (claim 37). U.S. Patent No: 5780024 disclose embodiments having 2 or 8 additional amino acids (col 6) and indicate that more or less are encompassed by the invention, and can be added, particularly as a matter of convenience in the cloning process, e.g. col 6, lines 37-40. However, Halpern et al. disclose the recombinant use of the tetanus toxin C-fragment including at least 9 amino acids of the B-fragment (second paragraph of the DISCUSSION on page 1007), and specifically teach that its probable that it is the addition of these amino acids of the B-fragment that results in the improved neuronal binding properties of the C-fragment, see page 1007, col 2, paragraph. Furthermore, Halpern teach that the addition a much greater portion of the B-fragment (e.g. 121 amino acids) might cause the undesirable property of insolubility, see page 1007, Col 2, 3rd paragraph. However Halpern also teach that a small number of amino acids, in addition to the nine residues of the B-fragment, may also aid in the improvement of the binding properties, e.g. the fragment used by Halpern contains and an additional 8 residues encoded by the vector, see second paragraph of the DISCUSSION on page 1007. Thus, the skilled would have looked to optimize the size of the additional B-fragment sequences as differing not much than the nine residues taught by Halpern but perhaps as much as 17 residues. Therefore, at the time the instant invention was made, it would have been an obvious matter of routine optimization of operating parameters to use nine, ten, eleven, etc. additional amino acids of the B-fragment (as taught by Halpern) when practicing the invention disclosed in U.S. Patent

No: 5780024 The motivation to do so was provided by both U.S. Patent No: 5780024, wherein it was taught that additional amino acids of the B-fragment may be added to the C-fragment as a matter of routine optimization, and Halpern et al. who teach that additional amino acids of the B-fragment may enhance the binding of the C-fragment to neuronal membranes, such activity being obviously important in the practice of the invention of U.S. Patent No: 5780024, e.g. see col 1, lines 64-col 2 line 9 of U.S. Patent No: 5780024 .

Applicant argues that the '024 patent only speculates that the protein would be transported trans-synaptically yet the disclosure of the '024 patent demonstrates only retrograde (intra-cellular) transport (Example col 16). Specifically, Applicant argues that the '024 fusion peptide is expected to behave similarly to Applicant's fusion peptide in that Applicant's fusion peptide undergoes rapid retrograde transport within the neuron but needs more than 24 hours to travel transynaptically. The Example at col 16 was conducted for only 24 hours; not enough time for transynaptic transport. This argument has been fully considered but not deemed persuasive. The examiner agrees with the factual statements in the argument, however the '024 patents specifically teaches the use of the fusion peptide for the treatment of people, e.g., col 20, and one of ordinary skill in the art certainly would not section the brains of such people after 24 hrs as had been done to the mice in the Example at col 16. Rather, as specifically taught in the '024 patent, the fusion peptide is expected to undergo "transynaptic transfer between neurons", see col 4, lines 34-44.

Citing case law, applicant argues that because the '024 patent does not disclose transynaptic transport, the Office must provide a prior art reference that discloses this element in order to make a *prima facie* case of obviousness. This argument has been fully considered but

not deemed persuasive for several reasons. First, '024 patents specifically discloses transynaptic transport, see col 4, lines 34-44. Second, the rejection is not based on the obviousness of transynaptic transport – such is specifically taught in the '024 patent. The prima facie case for transynaptic transport comes directly from the teachings of the '024 patent. Applicant has presented no arguments as to why one skilled in the art would doubt the validity of the teachings of the '024 patent. Since the Patent Office does not have a laboratory to test the reference peptides, it is Applicant's burden to show that the reference polypeptides do not possess the required transynaptic transport activity. See In re Best, 195 USPQ 430, 433 (CCPA 1977); In re Marosi, 218 USPQ 289, 292-293 (Fed. Cir. 1983); and In re Fitzgerald et al., 205 USPQ594 (CCPA 1980).

Applicant's addressess the confusion regarding Kuypers et al., specifically, At page 16 of the Brief, Applicant alleged that the specification at pages 2-4 teaches that others have failed to show trans-synaptic transport. This argument was found unpersuasive by the examiner, because although the staining of second order neurons was week it could be detected in certain synaptically connected neurons (see the instant specification at page 3 bridging page 4. This statement in the specification is a clear admission that the C-terminal fragment was trans-synaptically transported.

Applicant argues that Halpren could not have provided the motivation to choose at least 11 amino acids of the B-fragment, because even three years latter, Halpren did not understand what factors affect retrograde transport. This argument has been fully considered but not deemed persuasive. Halpern teach that a small number of amino acids, in addition to the nine residues of the B-fragment, may also aid in the improvement of the binding properties, see

second paragraph of the DISCUSSION on page 1007. Thus, one would simply follow the teachings of Halpren, regardless of the exact mechanism through which it worked were known.

Claims 9 and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No: 5780024 in view of Halpern et al., Infection and Immunity, 58(4)1004-1009, April 1990, as applied to claims 1-8, 11 and 31, above, and in further view of Fishman et al., J. Neurological Sciences 98(311-325)1990, as set forth previously and reiterated below.

Claims 9 and 10 require a method as claimed in claims 6-8 as discussed above, yet claims 9 and 10 also require that the composition comprise at least two of said second molecules (claim 9) or that the said second molecule be located upstream of the tetanus toxin fragment. Fishman et al. teach that a second biologically active molecule can be conjugated to the tetanus C-fragment multiple times throughout the length (upstream or downstream) of the C-fragment (see page 313, middle paragraph and Figure 1, lanes 2 and 3). Therefore, it would be an obvious matter of routine optimization of operation parameters to incorporate at least two biologically active molecules to the C-fragment of the tetanus toxin, wherein at least one was associated upstream of the C-fragment, as taught by Fishman et al. when practicing the method of U.S. Patent No: 5780024 with the motivation to add amino acids of the B-fragment as taught by Halpern et al., as discussed above. The motivation to do so is provided by Fishman et al. who teach that multimeric complexes are desirable (page 13 middle paragraph). Fishman et al., also provide the artisan with a reasonable expectation of success because Fishman et al. teach that the large size of such complexes does not interfere with the uptake of the complexes into neurons (page 322, middle paragraph).

Applicant argues that the teachings on page 323 of Fishman et al., wherein Fishman et al clearly state that linkage of the C-fragment of tetanus toxin to another protein may enhance the stability of a chosen protein within the CNS as well as promote its spread by transynaptic transport, is merely speculative and would thus dissuade one from making the claimed invention. This argument has been fully considered but not deemed persuasive. One of ordinary skill in the art appreciates that the teachings of Fishman provide the expectation that the fusion protein is transported transynaptically, absent evidence to the contrary.

Claims 1-5, 8, 11, 31, 33-36 are also rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No: 5780024 in view of Halpern et al., Infection and Immunity, 58(4)1004-1009, April 1990, as applied to 1-8 , above, and in further view of U.S. Patent No: 6159948, as set forth previously and reiterated below.

Applicant's elected species of SMN (claim 8) is not taught by either U.S. Patent No: 5780024 or Halpern et al, as discussed above, however U.S. Patent No: 6159948 teaches the treatment of neurodegenerative disorders (e.g. spinal muscular atrophy, col 1) comprising the administration of the SMN protein (a.k.a NAIP) wherein the SMN protein is a fused to tetanus toxin or a fragment thereof (see col 21, last paragraph). Therefore, it would have been obvious to one of ordinary skill in the art, at the time the invention was made, with reasonable expectation of success to modify the C-fragment of tetanus toxin as taught by Halpern and by U.S. Patent No: 5780024, as discussed above, with the SMN protein as taught by U.S. Patent No: 6159948, for use in a method to deliver the SMN protein to the central nervous system. The motivation to do so was provided by U.S. Patent No: 6159948 wherein it is stated that increased

levels of SMN protein (NAIP) can provide neuroprotection against neurodegenerative diseases (see the Abstract, and col 1), wherein the SMN protein should be fused to tetanus toxin or a fragment thereof (see col 21, last paragraph).

Applicant's arguments regarding Patent No: 5780024 have been addressed above.

Claims 1-5 8, 11, 31, 34 and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Francis et al. J. Biol. Chem. 270(25)15434-15442, 1995, in view of Halpern et al., Infection and Immunity, 58(4)1004-1009, April 1990, as set forth previously and reiterated below:

Francis et al. disclose an in vitro method for delivery of a composition (SOD:Tet451), comprising a tetanus toxin C fragment recombinantly fused to a second protein (e.g. SOD-1, see the Abstract), wherein said second protein is fused downstream to the tetanus toxin C fragment (see col 6) and wherein, absent evidence to the contrary, the fusion protein is capable of in vivo retrograde axonal transport and transynaptic transport in to the CNS (e.g. from systemic administration to the brain stem, see page 15434). Francis et al. did not use the method for in vivo delivery, however they proposed to do so (see the Abstract, for example). Further, Francis et al disclosed that the method could be used in the treatment of neurodegenerative diseases of the CNS (15434 see col 1 for example). Therefore, it would have been obvious to one of ordinary skill in the art, at the time the invention was made to with reasonable expectation of success to use the in vitro method of delivery disclosed by Francis et al. for in vivo delivery, as required by the instant claims. The motivation to do so was provided by Francis et al. who state the tetanus toxin has a well documented capacity for neuronal binding and internalization. In particular when administered systemically or intramuscularly to animals, the toxin is taken up

selectively by motor neurons in the brain stem and spinal chord. The C-fragment retains these properties without the toxic domain (see 15434 see col 1). Further, Francis et al. hypothesize that their disclosed fusion protein could increase the delivery of the SOD-1 protein to the central nervous system in general and motor neurons in particular, potentially providing effective enzyme therapy to neurons (see 15434 see col 1).

Francis et al. disclose that it is the C-fragment of tetanus that provides for neuronal binding and internalization without toxicity, yet Francis et al. do not disclose, specifically that the C-fragment should contain at least 11 amino acids of the B-fragment. Halpern et al. disclose the recombinant use of the tetanus toxin C-fragment including at least 9 amino acids of the B-fragment (second paragraph of the DISCUSSION on page 1007), and specifically teach that its probable that it is the addition of these amino acids of the B-fragment that results in the improved neuronal binding properties of the C-fragment, see page 1007, col 2, paragraph. Furthermore, Halpern teach that the addition a much greater portion of the B-fragment (e.g. 121 amino acids) might cause the undesirable property of insolubility, see page 1007, Col 2, 3rd paragraph. However Halpern also teach that a small number of amino acids, in addition to the nine residues of the B-fragment, may also aid in the improvement of the binding properties, e.g. the fragment used by Halpern contains and an additional 8 residues encoded by the vector, see second paragraph of the DISCUSSION on page 1007. Thus, the skilled would have looked to optimize the size of the additional B-fragment sequences as differing not much than the nine residues taught by Halpern but perhaps as much as 17 residues. Therefore, at the time the instant invention was made, it would have been an obvious matter of routine optimization of operating parameters to use nine, ten, eleven, etc. additional amino acids of the B-fragment (as taught by

Halpern) when practicing the method taught and proposed by Francis et al. The motivation to do so was provided by Halpern et al. who teach that additional amino acids of the B-fragment may enhance the binding of the C-fragment to neuronal membranes, such activity being obviously important in the practice of the method taught and suggested by Francis et al..

Applicant argues that Francis et al. do not disclose in vivo transynaptic transport. This argument has been fully considered but not deemed persuasive. Referring to the uptake of the fusion protein by motor neurons, at page 15441, col 1, last sentence of the first full paragraph, Frances et al. teach ∀through this pathway, the hybrid protein could access other central nervous system neurons as well, given the ability of TTC to undergo retrograde trans-synaptic transfer". Thus, Frances et al. specifically assert that hybrid protein is capable of transynaptic transport. Applicant has provided no reasons as to why one of ordinary skill in the art would not believe the teachings of Frances et al.

Claims 8, 11, 31, 33, 35, 36 are also rejected under 35 U.S.C. 103(a) as being unpatentable over Francis et al. J. Biol. Chem. 270(25)15434-15442, 1995 in view of Halpern et al., Infection and Immunity, 58(4)1004-1009, April 1990, as applied to 1-8 , above, and in further view of U.S. Patent No: 6159948, as set forth previously and reiterated above.

Applicant's elected species of SMN (claim 8) is not taught by either Francis et al. or Halpern et al, as discussed above, however U.S. Patent No: 6159948 teaches the treatment of neurodegenerative disorders (e.g. spinal muscular atrophy, col 1) comprising the administration of the SMN protein (a.k.a NAIP) wherein the SMN protein is a fused to tetanus toxin or a fragment thereof (see col 21, last paragraph). Therefore, it would have been obvious to one of

ordinary skill in the art, at the time the invention was made, with reasonable expectation of success to modify the C-fragment of tetanus toxin as taught by Halpern et al. and by Francis et al., as discussed above, with the SMN protein as taught by U.S. Patent No: 6159948, for use in a method to deliver the SMN protein to the central nervous system. The motivation to do so was provided by U.S. Patent No: 6159948 wherein it is stated that increased levels of SMN protein (NAIP) can provide neuroprotection against neurodegenerative diseases (see the Abstract, and col 1), wherein the SMN protein should be fused to tetanus toxin or a fragment thereof (see col 21, last paragraph).

Applicant's arguments regarding Halpern, Francis and the '948 patent have been addressed above.

Conclusion

The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1649.

Please note the new central fax number for official correspondence below:

This application contains claims 12-30, 32 drawn to an invention nonelected with traverse in Applicant's response of 8/3/01. A complete reply to the final rejection must include cancelation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

No claims are allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX months.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Brannock, Ph.D., whose telephone number is (571) 272-0869. The examiner can normally be reached on Mondays through Fridays from 10:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres, Ph.D., can be reached at (571) 272-0867. Official papers filed by fax should be directed to **571-273-8300**.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

MB

Elizabeth C. Kemmerer

ELIZABETH KEMMERER
PRIMARY EXAMINER

January 4, 2005